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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The primary aim is to determine the efficacy (comparing 6 month GOSE) of two dosing regimens of TXA initiated in the pre-hospital setting in patients with moderate to severe TBI (GCS score 3-12).The first year has been spent in preparation for study implementation including approvals by the ROC Protocol Review Committee and Data, Safety Monitoring Board, as well as obtaining an FDA IND and Health Canada CTA. The documents for the first site approval were sent to HRPO on June 19, 2014 and final approval by the Sec. Army is still pending. The blinded study drugs were manufactured and packaged into study kits. A web data entry system to collect the patient data and check for errors (and a detailed Manual of Operations) is being beta tested. An inventory management system to track the study kits and lab/CT/MRI scan data is ready. Training materials have been finalized in order to train the EMS and hospital staff on the study. Ten of 12 sites have submitted the protocol for IRB approval and are either conducting community consultation or have completed it. Five sites have final approval and await HRPO approval before training their EMS and hospital staff.

15. SUBJECT TERMS
Traumatic Brain Injury (TBI), TXA, prehospital

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1. **Introduction**

The primary aim of this exception from informed consent study is to determine the efficacy of two dosing regimens of TXA compared to placebo initiated in the prehospital setting in patients with moderate to severe TBI (GCS score ≤12) using the 6 month GOSE. The secondary aims are to compare TXA to placebo in clinical outcomes (ICH progression, Marshall and Rotterdam CT classification scores, DRS at discharge and 6 months, GOSE at discharge, 28 day survival, frequency of neurosurgical interventions and ventilator-free , ICU-free, and hospital-free days), safety outcomes (seizures, cerebral ischemic events, myocardial infarctions, deep venous thrombosis and pulmonary thromboembolism) and mechanistic outcomes (alterations in fibrinolysis based on fibrinolytic pathway mediators and degree of clot lysis based on TEG).

2. **Body**

Scope of Work

a. Specific Aim 1-to determine clinical efficacy of TXA in TBI as measure by multiple clinical endpoints

i. Major Subtask 1.a.: Obtain regulatory approval by PRC, FDA, DSMB, UW IRB, Health Canada, HRPO/Dod/ACURO

This subtask has been completed except for final regulatory approval by HRPO/Dod/ACURO. The first IRB approved clinical enrolling site documents were sent to HRPO on 6/19/2014. As of 9/10/2014 we believe that the documents are in the process of being reviewed and signed by the Sec. Army.

ii. Major Subtask 1.b.: Clinical Site submission to and approval from IRB including community consultation/notification.

In order to increase enrollment the Data Coordinating Center contacted and screened several additional institutions resulting in the addition of two extra enrolling sites (an original site dropped out and was replaced by a new site). Below is a table noting the start-up status of each site.

Site	IRB submitted	Final Approval after Community Consultation (CC) & Notification	Amendment 1	Training of EMS	Documents ready to be sent to HRPO
UW DCC	3/17/2014	4/9/2014	10/4/2014 submitted answers to questions	N/A	N/A not enrolling site
Toronto- 2 hospitals	2/2014	3/2014			
Alabama- 1 hospital	5/8/2014	CC done, submitting 10/23	Submitting 10/23		
British Columbia-	6/5/2014	10/13/2014			

2 hospitals					
Cincinnati, OH 1 hospital	5/9/2014	Submitted CC results			
Dallas/Ft. Worth 6 hospitals	4/16/2014	6/19/2014	9/19/2014		6/19/2014 finalized 9/102014
Houston, TX 1 hospital	7/9/2014	Started CC, not yet finished			
Milwaukee, WI 1 hospital	5/14/2014	Conducting CC			
Mayo Clinic, MN 1 hospital	Application not yet submitted				
Portland, OR 1 hospital	5/7/2014	Finished CC. Submitting 10172014	10/17/2014		
Seattle/King Co, WA 1 hospital	5/23/2014	9/24/2014	Need DCC approval first	Began 8/2014	
St. Paul, MN 1 hospital	5/15/2014	9/14/2014		10/11/2014 will do refresher	
Hennepin Co, MN 1 hospital	Application not yet submitted				

iii. Major Subtask 2.a.: Study implementation

a. Designing data collection forms
Case forms have been designed with input from investigators and clinical sites.

b. Web programming of forms, imaging/lab reporting, monitoring
Web programming is completed and the forms are being beta tested. Error checks are in place and being optimized as needed. The only outstanding form is for additional data collection by the OHSU staff in reviewing the CT/MRI scans. Draft monitoring reports have been created and were presented to the DSMB in April 2014. Monitoring criteria have been developed and presented to the Study Monitoring Committee (internal committee of ROC investigators and data coordinating center staff charged with monitoring the study).

c. Training EMS/hospital staff
Training materials have been finalized for training of both the EMS and the hospital staff. Two sites have begun training as some EMS agencies have set times of the year for training. Other sites are waiting until final HRPO to train so that additional refresher training is not needed.

d. Hire and train research staff on protocol

Main coordinators continue to have biweekly calls to discuss study issues (one with investigators and one with only coordinators). Formal training on the protocol and data collection forms is upcoming in October, 2014 with a webinar that will also be recorded for future training. Additionally each site will have a detailed start-up checklist completed and approved by the Study Monitoring Committee prior to enrolling patients and calls as needed with DCC clinical and regulatory personnel to ensure completion of milestones. Included on this checklist is special documentation for and approval by HRPO.

The items below have not been completed:

e. Enroll 1002 subjects-insert enrollment table
f. Site audits
g. Cleaning and analyzing data
h. CT scan reviews, ICH measurements-training of tech
i. Statistical analyses
j. Manuscript preparation

b. Specific Aim 2: Determine the safety of TXA in TBI

i. Major Subtask 1: Appoint Medical Monitor

Dr. Eugene Moore has accepted the role of Medical Monitor and a call was conducted to review the protocol and his role as Medical Monitor. Another call will be conducted once the study is close to starting.

ii. Major Subtask 2: Collection and review of safety endpoint

Forms have been programmed to collect SAE data after enrollment begins. A process has been developed to unblind a patient if needed.

iii. DSMB meetings every 3-6 months

DSMB has approved the protocol and the monitoring tables and will review the data every 3 months once the study starts.

c. Specific Aim 3: Explore the mechanism of TXA

i. Major Subtask 1: Collect TEG at sites

All hospitals except three will be able to collect TEG measurements. It is estimated that this will reduce the sample by approximately 60 patients. The DCC was successful in obtaining three loaner TEG machines so that some hospitals will be able to obtain TEGs. In addition, the DCC was also able to get a reduction in the cost of the TEG supplies and the study will be able to purchase and ship these to the sites.

ii. Major Subtask 2: Conducting assays on blood-OHSU

The OHSU coordinating center has completed their meetings with the Diagnostica Stago company personnel in defining what tests to run for the study and how to conduct the analyses. OHSU is purchasing supplies to send to the clinical sites for blood sample collection. Laboratory staff has been identified to completing the lab assays. A draft MOP for lab processing is completed and being finalized.

Dr. Susan Rowell submitted an R01 application to NHLBI in May 2014 to obtain additional funding to examine circulating biomarkers of structural

brain injury in the patients enrolled in the TXA trial. This funding would also provide for the creation of a genomic and transcriptomic repository as well as for pharmacokinetic analyses. The study section met in August and the proposal received a score that is potentially in the fundable range. The council meeting will occur in late October and she anticipates a decision in November. Dr. Rowell has also received a commitment from the Solomon Trust Foundation to provide funding to establish the genomic repository if the R01 is not funded.

3. Key Research Accomplishments

The research accomplishments are related to planning and start-up of the study and include:

10/24/2013 FDA IND approval
10/30/2013 Registration on ClinicalTrials.gov
11/22/2013 Contract with Custo/Excella pharma to produce intervention materials
11/27/2013 Contract with ALMAC to produce study kits, store and mail kits to sites
12/19/2013 ROC Protocol Review Committee approval
03/14/2014 ROC DSMB approval
03/15/2014 Draft case report forms completed, programming started
03/20/2014 Health Canada no objection letter
03/22/2014 In-hospital Pharmacy procedures completed
04/16/2014 Draft monitoring tables presented to the ROC DSMB
05/23/2014 Amendment 1 to protocol which include ancillary study (storage for future genetic testing and biomarkers)
05/28/2014 Study drugs manufactured/shipped to ALMAC for packaging
06/03/2014 Certificate of Confidentiality obtained
06/10/2014 Web-based inventory system completed
06/19/2014 First IRB approved site materials sent to HRPO
06/26/2014 OHSU finalizes blood analysis procedures, continues working on CT/MRI
06/30/2014 Pharmacy SOPs final and final draft of EMS training materials
08/14/2014 ALMAC completed study kits and identity testing (ready to send to sites)
08/25/2014 Final draft of TXA benchmarks developed (to go to SMC for approval)
09/09/2014 Amendment 1.1 to protocol which includes a minor correction
09/10/2014 HARPO indicates packet complete and moving through approval process
09/15/2014 EMS/hospital training materials completed
09/30/2014 Form web programming completed except for OHSU CT/MRI data collection

4. Reportable Outcomes

There are no reportable outcomes yet. The group will prepare a methods paper to be submitted to a journal in the next six months.

5. Conclusions

The ROC DCC and clinical sites are poised to begin enrollment as soon as the Sec. Army approves the study. This study will likely require follow-up to be conducted into 2016 and the NHBLI has assured the investigators that a no cost extension will be approved for 2016 in order to complete the study.

6. References-N/A

7. Appendices-N/A

Early Tranexamic Acid Use for Traumatic Brain Injury

DMRDP Funding Opportunity Number: W81XWH-12-CCCJPC-TACR

PI: Susanne May, PhD; Schreiber/Rowell, MD **Org:** University of Washington; OHSU Total Award: 4.054M

Study Aims – in subjects with traumatic brain injury:

To determine if 1gm bolus TXA followed by 1gm infusion over 8 hrs, or, a single 2 gm bolus TXA improves the following compared to placebo:

1.Global neurologic outcome at 6 months by Glasgow Outcome Scale Score (GOS-E)
2.28-day mortality
3.Progression of intracranial hemorrhage

To determine the safety of TXA as measured by:

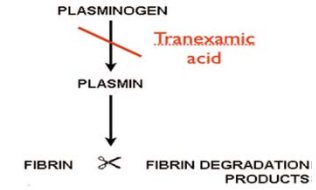
1.Thromboembolic events (cerebral ischemic events, MI, DVT, PE)
2.Seizures

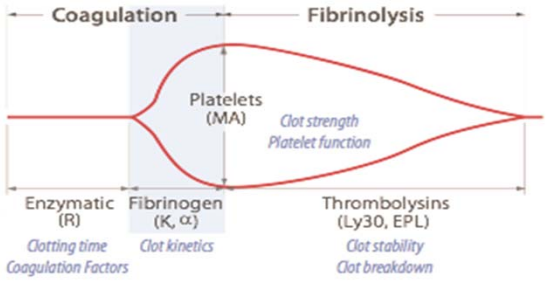
To explore the mechanism of TXA via:

1.Thrombelastography
2.Analysis of coagulation pathway mediators

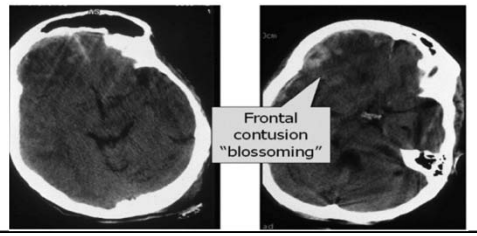
Approach – to be conducted under EFIC

Phase II multi-site randomized placebo controlled trial evaluating the safety and efficacy of 2 dosing regimens of TXA administered within 2 hours of injury to patients with traumatic intracranial hemorrhage.





Progression of Injury



Timeline and Cost

Activities / CY	13-14	14-15	15-16
Regulatory approval: ROC/FDA/IRB			
EFIC requirements/ Final approval			
Enrollment and follow-up			
Data analysis and submission of primary paper			
Estimated Budget ($K) Total	**$256**	**$2585**	**$1214**

Updated: Oct 14, 2014, U of W, Seattle, WA

Goals/Milestones

CY13 Goal Regulatory approval

☑ Submit to ROC PRC ☑ PRC approval
☑ Submit to ROC DSMB ☑ Submit to FDA for IND
☑ IND final approval ☑FDA

CY14 Goals EFIC requirements/enrollment begins

☑ Sites-DCC submit for IRB approval ☑ DSMB approval
☑ Submit for Health Canada approval ☑ approval
☑ Sites begin community consultation
☑ Sites begin public notification
☑ Web data entry completed
☐All sites begin enrollment

CY15 Goal Completion of enrollment/data analysis begins

☐ Complete patient enrollment at all sites
☐ Begin data analysis/clean up

CY16 Goal Completion of analysis/primary paper submitted

☐ Last follow-up completed
☐ Analysis final
☐ Primary paper submitted